REPORT DOCUMENTATION PAGE

Form Approved OMB NO. 0704-0188

1. REPORT DATE (DD-MM-YYYY)	2. REPORT TYPE	3. DATES COVERED (From - To)
	New Reprint	-

4. TITLE AND SUBTITLE

Adaptive Control of Bivalirudin in the Cardiac Intensive Care Unit

5a. CONTRACT NUMBER	W911NF-12-1-0390
5b. GRANT NUMBER	
5c. PROGRAM ELEMENT NUMBER	611103
5d. PROJECT NUMBER	
5e. TASK NUMBER	
5f. WORK UNIT NUMBER	

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS (ES)

U.S. Army Research Office
P.O. Box 12211
Research Triangle Park, NC 27709-2211

10. SPONSOR/MONITOR'S ACRONYM(S)
ARO

11. SPONSOR/MONITOR'S REPORT NUMBER(S)
61789-MA-MUR.51

12. DISTRIBUTION AVAILIBILITY STATEMENT

Approved for public release; distribution is unlimited.

13. SUPPLEMENTARY NOTES

The views, opinions and/or findings contained in this report are those of the author(s) and should not contrued as an official Department of the Army position, policy or decision, unless so designated by other documentation.

14. ABSTRACT

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15. SUBJECT TERMS

Bivalirudin, Pharmacokinetics, Parameter Iden- tification, Adaptive Control

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	15. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			Claus Wilke
UU	UU	UU	UU		19b. TELEPHONE NUMBER 512-471-6028

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REPORT DOCUMENTATION PAGE (SF298)
(Continuation Sheet)

Continuation for Block 13

ARO Report Number 61789.51-MA-MUR
Adaptive Control of Bivalirudin in the Cardiac Int...

Block 13: Supplementary Note

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Adaptive Control of Bivalirudin in the Cardiac Intensive Care Unit*

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***Abstract*—Bivalirudin is a direct thrombin inhibitor used in the cardiac intensive care unit when heparin is contraindicated due to heparin-induced thrombocytopenia. Since it is not a commonly used drug, clinical experience with its dosing is sparse. In earlier work ([1]) we developed a dynamic system model that accurately predicts the effect of bivalirudin given dosage over time and patient physiological characteristics. This paper develops adaptive dosage controllers that regulate its effect to desired levels. To that end, and in the case that bivalirudin model parameters are available, we develop a Model Reference Control law. In the case that model parameters are unknown, an indirect Model Reference Adaptive Control scheme is applied to estimate model parameters first and then adapt the controller. Alternatively, direct Model Reference Adaptive Control is applied to adapt the controller directly without estimating model parameters first. Our algorithms are validated using actual patient data from a large hospital in the Boston area.**

***Index Terms*—Bivalirudin, Pharmacokinetics, Parameter Identification, Adaptive Control.**

I. Introduction

The US health care system is viewed as costly and highly inefficient. Among the many reform efforts, the meaningful use of Electronic Health Records (EHRs) is invariably seen as a key to improving efficiency. In the hospital, the digitization of data from medical devices enables the development of algorithms that can automate decision making and facilitate treatment. This is exactly the goal of this paper which focuses on automating dosage decisions for a particular drug –bivalirudin– used in the cardiac Intensive Care Unit (ICU).

Bivalirudin antagonizes the effect of thrombin in the blood clotting cascade, thereby preventing complications from blood clotting. It is currently FDA-approved for short-term anticoagulation of patients undergoing cardiac catheterization to prevent complications due to undesired blood clots [2], [3], [4], [5]. Bivalirudin is administered to patients who have a contraindication to heparin. It is infused continuously, and is eliminated via the kidney and by plasma protease-metabolism. It affects the coagulation parameters *Partial Thromboplastin Time (PTT)* and the *International Normalized Ratio (INR)* in a dose-dependent fashion. The PTT value is measured in seconds and it will be used as the output one wishes to regulate within a specific range.

Although not commonly used overall, bivalirudin is finding increasing use in the ICU. Residents adjusting the infusion rate of bivalirudin may have limited experience, thus, risking over- or under-dosing. Currently, the drug is regulated empirically or with a very simple nomogram [6]. Adequate anticoagulation is necessary to avoid the risk of clot formation, but overshooting increases the risk of bleeding. Complicating matters, there is considerable inter- and intra-individual variability in the response to bivalirudin. Motivated by these challenges, in earlier work [7], [8], [1], we developed methods for predicting future PTT values given past infusion rates and the patient's renal and liver function characteristics. Related work has used pharmacokinetic-pharmacodynamic models to model the effect of various drugs, see, e.g., [9], [10]. One of our methods in [1] proposes an explicit dynamic system model which was shown to produce quite accurate results when tested against actual patient data.

In this paper, we pursue what we view as the natural next step. Leveraging the dynamic system model from [8], [1], we seek to synthesize controllers that can regulate the infusion rate to drive PTT within a desirable range. Other methodologies such as expert systems have also been used for controlling some drugs [11]. We develop two types of control laws. First, assuming that a dynamic system model that can predict PTT given dosage is completely characterized, we develop a *Model Reference Control (MRC)* law. Model parameters, however, may be viewed as not known with certainty, which is due to modeling errors and inter- or intra-individual variability. To overcome this problem, we develop an indirect *Model Reference Adaptive Control (MRAC)* law that identifies the model parameters first and then adapts the controller in real-time. Furthermore, we develop a direct Model Reference Adaptive Control law that adapts the controller directly without estimating model parameters first, which is more efficient. For each case, we present analytical and numerical evidence showing that the controllers do drive PTT to the desirable range. Our numerical validation is in fact done using actual patient data from the Brigham and Women's Hospital – a large hospital in the Boston area.

The remainder of the paper is organized as follows. Sec. II presents the dynamic system model that predicts the effect of bivalirudin given dosage and patient physiological information. Sec. III presents the proposed control schemes; Sec. III-A de-

* Research partially supported by the NIH/NIGMS under grant R01-GM093147, by the NSF under grants CNS-1239021 and IIS-1237022, by the ARO under grants W911NF-11-1-0227 and W911NF-12-1-0390, by the ONR under grant N00014-10-1-0952, and by the STAR (Surgical ICU TrAnslational Research) Center at Brigham and Women's Hospital.

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velops the MRC law whereas Sec. III-B develops the indirect MRAC law based on the patient model but with unknown parameters. Sec. III-C develops the direct MRAC, which is more efficient in adapting the controller. Finally, concluding remarks appear in Sec. IV.

Notation: We use bold letters to denote vectors and matrices; typically vectors are denoted by lower case letters and matrices by upper case letters. Vectors are assumed to be column vectors unless explicitly stated otherwise. For economy of space we write $\mathbf{x} = (x_1, \cdots, x_n)$ for the column vector $\mathbf{x} \in \mathbb{R}^n$. In addition, we use lower case letters to denote time domain functions (e.g., $f(t)$), and upper case letters to denote Laplace transforms (e.g., $F(s)$).

II. Dynamic System Model Formulation

A. The Model

This section presents a *Multiple Input Single Output (MISO)* dynamic system model that attempts to explicitly account for the way bivalirudin affects PTT in patients. The model was developed and validated in [1]; it is presented here briefly to establish the notation and to set the stage for the control schemes of Sec. III.

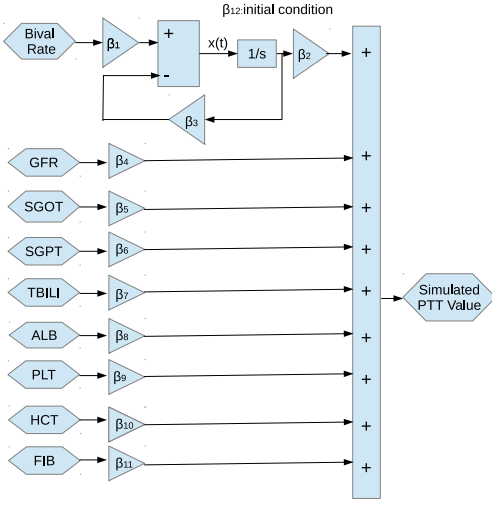

Fig. 1. The Multiple Inputs Single Output (MISO) dynamic system model.

The key quantity (response) we would like to predict is the PTT at each time t. The dynamic model structure is shown in Fig 1. There are 9 inputs which are denoted by $u_i(t)$, $i = 1, \ldots, 9$ and correspond to important physiological variables used as predictors. More specifically, inputs $u_1(t), \ldots, u_9(t)$ respectively correspond to:

1) **Bival rate** (mg/kg/h): the weight-based bivalirudin injection rate.
2) **GFR** (mL/min): the glomerular filtration rate.
3) **SGOT** (Units/L): the Serum Glutamic Oxaloacetic Transaminase.
4) **SGPT** (Units/L): the Serum Glutamic Pyruvic Transaminase.
5) **TBILI** (mg/dL): total bilirubin.
6) **ALB** (g/L): Albumin.
7) **PLT** (K/mcL): Platelet count.
8) **HCT** $(\%)$: Hematocrit.
9) **FIB** (mg/dL): Fibrinogen.

More detailed description of these physiological variables can be found in [1].

The model of Fig. 1 has a single output –the PTT value– which is denoted by $y(t)$. There is also a single state variable denoted by $x(t)$. Overall there are 12 unknown parameters: 11 of which correspond to the various gains and are denoted by β_i, $i = 1, \ldots, 11$. The initial condition of the system is the 12th unknown parameter and is denoted by $x(0)$ (β_{12}). The system dynamics are:

$$\begin{aligned} \dot{x}(t) &= \mathbf{A}x(t) + \mathbf{B}\mathbf{u}(t), \\ y(t) &= \mathbf{C}x(t) + \mathbf{D}\mathbf{u}(t), \end{aligned} \tag{1}$$

where $\mathbf{A} = -\beta_3$, $\mathbf{B} = [\beta_1 \ 0 \ \cdots \ 0]$, $\mathbf{C} = \beta_2$, and $\mathbf{D} = [0 \ \beta_4 \ \cdots \ \beta_{11}]$. Clearly, this is a *Linear Time Invariant (LTI)* dynamic system. The challenge is that we do not know the model parameters and we only have non-uniform sampled inputs $\mathbf{u}(t)$, and clinical observation values $y(t)$ at certain times t for each patient. It is therefore necessary to translate the continuous-time system dynamics to discrete-time dynamics before proceeding with parameter identification.

B. Parameter Identification

Given the highly non-uniform sampled data, two methods were introduced to identify model parameters in [1]. First, after converting to discrete-time dynamics, we formulated the parameter identification problem as the nonlinear optimization problem of minimizing some metric of fitness to a training set of sampled data.

The data set we used comes from the STAR (Surgical ICU Translational Research) Center at Brigham and Women's Hospital in Boston. It consists of records for 233 patients including the predictors and the output PTT value sampled (non-uniformly) over time. We randomly split our data set into a training set corresponding to $2/3$ of the total (155 patients) and a test set corresponding to $1/3$ of the total (78 patients). We use the former to identify the unknown system parameters and the latter to evaluate the performance of the various control laws we will develop in subsequent sections.

More specifically, let us use a subscript j to denote the model primitives, i.e., the state $x_j(t)$, output $y_j(t)$, and inputs $\mathbf{u}_j(t)$ for each patient $j = 1, \ldots, N$, where N denotes the number of patients in the training set. To distinguish between measurements of $y_j(t)$ and predictions based on the system dynamics we use $y_j(t)$ for the former and $\hat{y}_j(t)$ for the latter. Suppose for each patient j we have T_j measurements at times $t_j^1, \ldots, t_j^{T_j}$, where we adopt the convention $t_j^0 = 0$ for all j. We can then formulate a nonlinear optimization problem of minimizing the least squares error

$$\sum_{j=1}^{N} \sum_{t=t_j^1}^{t_j^{T_j}} (\hat{y}_j(t) - y_j(t))^2,$$

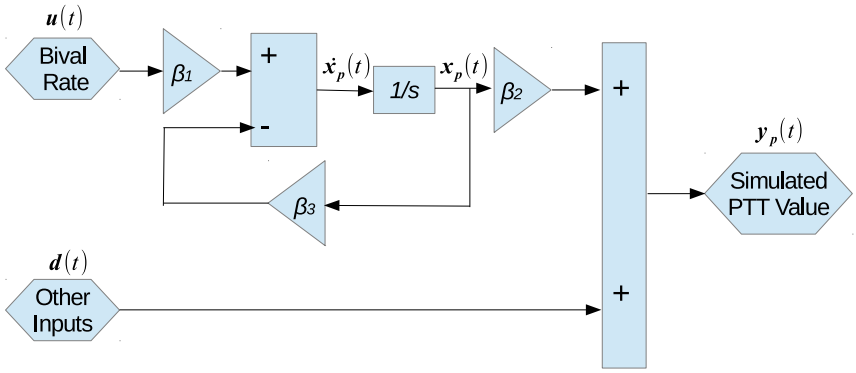

Fig. 2. In this dynamic model, the bivalirudin infusion rate $u(t)$ is the only controllable input. $d(t)$ is the linear combination of the rest of the inputs.

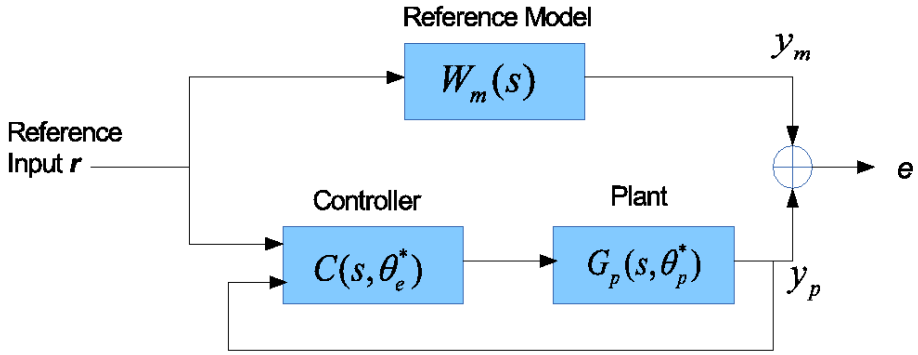

Fig. 3. Model Reference Adaptive Control (MRAC) structure.

subject to the discretized version of the system dynamics. The decision variables are $x(0)(= x(t_j^0)$ for all $j)$ and the parameters β_i, $i = 1, \ldots, 11$. One can easily substitute the expressions from the constraints (the system dynamics) into the objective function and obtain a nonlinear optimization problem with no constraints other than some bounds on the decision variables. This problem, however, is non-convex. We applied a Quasi-Newton method (BFGS) [12] to obtain optimal values for the model parameters. This yielded a population-wide model in the sense that its parameters produced the best fit with the sampled data. Furthermore, and to accommodate variability across patients, we used a recursive estimation method (Extended Kalman Filter) to estimate the parameter values that best fit a given individual patient in real-time.

III. Bivalirudin Control Scheme

We now turn to our primary goal of devising a proper controller to keep the PTT value in the range of 60s-80s. According to clinical experience, this range is safe and optimal for cardiac surgery patients. For the system we have defined in Eq. (1), note that the only controllable part is the bivalirudin infusion rate. The rest of the inputs are indicators of patients' liver (SGOT, SGPT, TBILI, ALB) and renal function (GFR) and include some metrics related to the blood (PLT, HCT, FIB). Arguably, these variables are not immediately affected by the drug but change over a longer time-scale than the one we focus on for controlling PTT through the infusion of bivalirudin. Therefore, we consider them as non-controllable and aggregate them in a variable $d(t)$ which is their linear combination with the appropriate gains $\beta_4, \ldots, \beta_{11}$ (see Fig. 2).

Ideally, we want to design a reference model which can generate sufficient but safe PTT values driven by a reference input signal. Based on the output of the reference model, we want to drive our system to perform similarly to the reference model by a proper control signal. Motivated by this, we adopt the so called continuous-time MRAC scheme. Fig. 3 shows the general structure of this control law. $W_m(s)$ denotes an ideal reference transfer function that can generate the desired reference output signal. The controllable system is represented by $G_p(s, \boldsymbol{\theta}_p^*)$, where $\boldsymbol{\theta}_p^*$ is a parameter vector. The objective is to design a controller $C(s, \boldsymbol{\theta}_e^*)$, parameterized by $\boldsymbol{\theta}_e^*$, to generate the proper control signals that can drive the controllable system to track the reference output values.

Our first controller is an MRC law that is designed assuming that the system parameters $\boldsymbol{\theta}_p^*$ are known.

A. Model Reference Control (MRC)

By observing the system in Fig. 2, we can rewrite the dynamics of a particular patient as

$$\dot{x}_p(t) = -\beta_3 x_p(t) + \beta_1 u(t), \tag{2}$$
$$y_p(t) = \beta_2 x_p(t) + d(t), \tag{3}$$

where we use $u(t), x_p(t), y_p(t)$ to denote the input signal (bivalirudin infusion rate), the state variable, and the output signal (PTT), respectively, and where $d(t) = \sum_{i=2}^{9} \beta_{i+2} u_i(t)$. Clinically, since the renal/liver functions and blood metrics of patients do not vary much within a certain period, we do not need to measure these physiological variables continuously and we assume that they are constant within the sample interval. By observing the clinical data, we find that $d(t)$ is a step-wise signal. Therefore, we assume that the first order derivative of $d(t)$ ($\dot{d}(t)$) is 0 within the sample interval. By taking the derivative on both sides of (3), using (2) to substitute for $\dot{x}_p(t)$, and using (3) to eliminate $\dot{x}_p(t)$, we obtain:

$$\dot{y}_p(t) = -\beta_3 y_p(t) + \beta_1\beta_2 u(t) + \beta_3 d(t). \tag{4}$$

In the frequency domain, we have

$$Y_p(s) = \frac{\beta_1\beta_2 U(s) + \beta_3 D(s)}{s + \beta_3},$$

where the system output $y_p(t)$ ($Y_p(s)$), the input $u(t)$ ($U(s)$), and $d(t)$ ($D(s)$) can be observed. Hence, in our setting, the system transfer function is $G_p(s, \boldsymbol{\theta}_p^*) = Y_p(s)/U(s)$ and it is parameterized by β_1, β_2 and β_3. In this case, $\boldsymbol{\theta}_p^* = (\beta_1, \beta_2, \beta_3)$.

Next, we design a reference transfer function $W_m(s)$. We take $W_m(s)$ to be a first-order LTI system driven by a reference signal $r(t)$:

$$W_m(s) = \frac{Y_m(s)}{R(s)} = \frac{b_m}{s + a_m},$$

which is equivalent to

$$\dot{y}_m(t) = -a_m y_m(t) + b_m r(t), \quad \text{or} \tag{5}$$
$$Y_m(s) = \frac{b_m}{s + a_m} R(s),$$

for any bounded piecewise continuous signal $r(t)$, where $a_m > 0$, $b_m \neq 0$ are known. We assume that a_m, b_m, and $r(t)$ are chosen so that $y_m(t)$ represents the desired output signal.

Before introducing the MRC law, we start with two definitions and a theorem (proven in the Appendix).

Definition 1
A state $\mathbf{x}_e$ *is said to be an* equilibrium state *of the system* $\dot{\mathbf{x}} = f(t, \mathbf{x})$, $\mathbf{x}(t_0) = \mathbf{x}_0$, *where* $\mathbf{x} \in \mathbb{R}^n, f : \mathscr{T} \times B(r) \to \mathbb{R}^n, \mathscr{T} = [t_0, \infty)$, $B(r) = \{\mathbf{x} \in \mathbb{R}^n \mid \|\mathbf{x}\| < r\}$, *if* $f(t, \mathbf{x}_e) \equiv 0\ \forall t \geq t_0$. *We assume that* f *is such that for every* $\mathbf{x}_0 \in B(r)$ *and every* $t_0 \in [0, \infty)$, *the system possesses one and only one solution* $\mathbf{x}(t; t_0, \mathbf{x}_0)$.

Definition 2
A equilibrium state $\mathbf{x}_e$ *is* exponentially stable *if there exits an* $\alpha > 0$ *and for every* $\epsilon > 0$ *there exists* $\delta(\epsilon) > 0$, *such that* $\|\mathbf{x}(t; t_0, \mathbf{x}_0) - \mathbf{x}_e\| \leq \epsilon e^{-\alpha(t - t_0)}$, $\forall t \geq t_0$ *whenever* $\|\mathbf{x}_0 - \mathbf{x}_e\| < \delta(\epsilon)$.

Theorem III.1 *If we choose* $a_m > 0$, $b_m \neq 0$, *and* $r(t) = C_r$ *(constant), the reference model equilibrium state* $y_{me} = \frac{b_m C_r}{a_m}$ *is exponentially stable.*

We will now design a proper controller $u(t)$ such that all signals in the closed-loop system are bounded and the system output $y_p(t)$ tracks the reference model output $y_m(t)$. The control law should be chosen so that the closed-loop plant transfer function from the input $r(t)$ to the output $y_p(t)$ is equal to the reference model transfer function. Motivated by this, we propose the control law

$$C(s, \boldsymbol{\theta}_e^*) = U(s) = -k_1^* Y_P(s) + k_2^* R(s) - k_3^* D(s),$$

or equivalently, in the time domain

$$u^*(t) = -k_1^* y_p(t) + k_2^* r(t) - k_3^* d(t), \tag{6}$$

where k_1^*, k_2^*, k_3^* are controller coefficients chosen so that

$$\frac{Y_p(s)}{R(s)} = \frac{b_m}{s + a_m} = \frac{Y_m(s)}{R(s)}. \tag{7}$$

Eq. (7) is satisfied, if we select

$$k_1^* = -\frac{1}{\beta_1\beta_2}(\beta_3 - a_m), \quad k_2^* = \frac{b_m}{\beta_1\beta_2}, \quad k_3^* = \frac{\beta_3}{\beta_1\beta_2},$$

which yields

$$u(t) = \frac{1}{\beta_1\beta_2}(\beta_3 - a_m) y_p(t) + \frac{b_m}{\beta_1\beta_2} r(t) - \frac{\beta_3}{\beta_1\beta_2} d(t), \tag{8}$$

provided of course that $\beta_1, \beta_2, \beta_3 \neq 0$, i.e., the system is controllable. Such a transfer function matching guarantees that $y_p(t) = y_m(t)$, $\forall t \geq t_0$, when $y_p(t_0) = y_m(t_0)$, or $|y_p(t) - y_m(t)| \to 0$ exponentially fast when $y_m(t_0) \neq y_p(t_0)$ for any bounded reference signal $r(t)$. We also note that, depending on the parameters of some patients, this law may yield a negative control signal which can not be implemented in practice (corresponds to "extraction of bivalirudin" from the patient). In such a case, we need to set a lower threshold of zero for the control signal. The final MRC control signal becomes $\max\{0, u(t)\}$ with $u(t)$ defined as in (8).

We test the performance of the MRC on the data set we described in Section II-B. We only use the test set (1/3 of the total) for testing since the remaining training set was used for model parameter identification. As mentioned before, $d(t)$ (the linear combination of physiological variables at time t) is a step-wise signal over time. By applying the parameter identification method outlined in Sec. II-B, we obtained both population-wide parameter values and individual model parameter values.

We tested the MRC control law on a subset of patients and the results were qualitatively the same in each case. We report results from a randomly selected patient who has identified model parameters and available input data. To that end, we set the reference parameters as $a_m = 10$, $b_m = 700$, $r(t) = 1$. Choosing these values keeps the reference PTT value to be 70s, which is in the middle of the desirable range. We note that these parameter values are simply an example and physicians

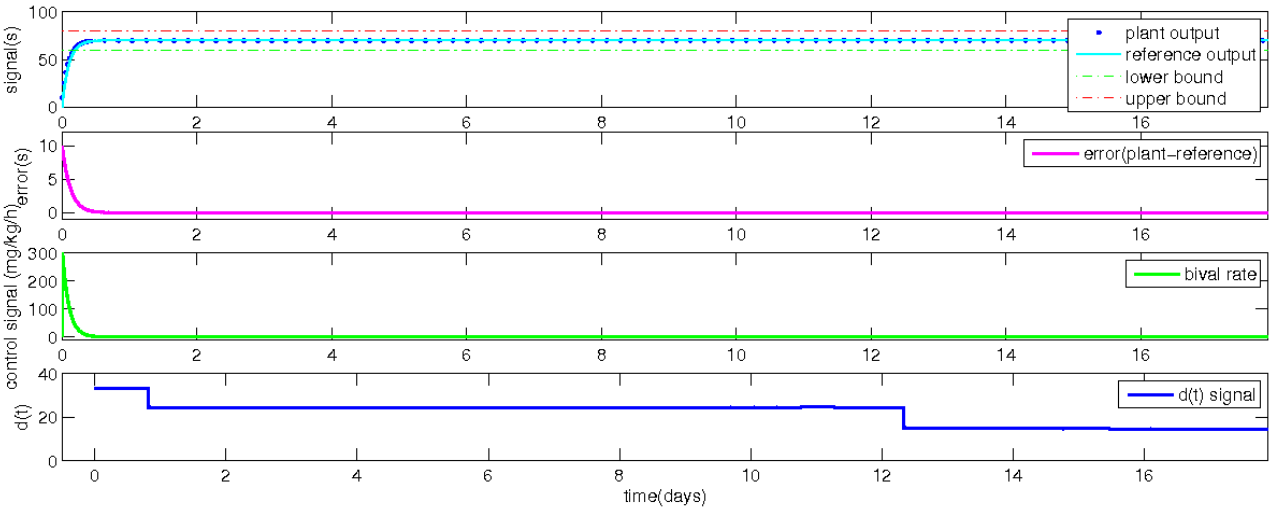

Fig. 4. The effect of the MRC law derived for and applied to one randomly selected patient.

have the freedom of selecting alternative values depending on the stable value and response time they wish to achieve.

The effect of the MRC law (8) on this randomly selected patient is shown in Figure 4. It can be seen that driven by inputs generated by the MRC law, the system output quickly converges to the reference output (top figure). The tracking error ($e(t) = y_p(t) - y_m(t)$) quickly converges to zero and remains at zero (second figure). We also obtain the control signal which corresponds to the bivalirudin infusion rate (third figure). The MRC control law we introduced is robust to the uncontrollable signal $d(t)$ (bottom figure). Although $d(t)$ changes over time, the control signal can adapt and drive the system to track the reference signal closely.

We next evaluate the performance of the MRC scheme on all patients in the test set we described earlier. For performance evaluation, we use three performance metrics. The first one is the Root Mean Square Error (RMSE), which for patient i is defined as

$$\mathrm{RMSE}_i = \sqrt{\frac{1}{T_i}\sum_{t=t_i^1}^{t_i^{T_i}} (y_p^i(t_i) - y_m^i(t_i))^2},$$

where $t_i^1, \ldots, t_i^{T_i}$ are the time instants at which we adapt the controller for patient i. We define RMSE for the whole population of patients as the average per patient RMSE, i.e., RMSE$= \frac{1}{N_t}\sum_{i=1}^{N_t} \mathrm{RMSE}_i$, where N_t is the number of patients in the test set. We also define σ_{Ei} to be the standard deviation of the errors $e^i(t) = y_p^i(t) - y_m^i(t)$, $t = t_i^1, \ldots, t_i^{T_i}$, of patient i. Similarly, we define σ_E as the average standard deviation of σ_{Ei}'s, i.e., $\sigma_E = \frac{1}{N_t}\sum_{i=1}^{N_t} \sigma_{Ei}$.

To capture a notion of "relative" error, we also compute the Normalized Root Mean Square Error (NRMSE) defined for each patient i as

$$\mathrm{NRMSE}_i = \sqrt{\frac{1}{T_i}\sum_{t=t_i^1}^{t_i^{T_i}} [(y_p^i(t_i) - y_m^i(t_i))/y_m^i(t_i)]^2}.$$

As with the RMSE, we define the population-wide NRMSE as the average of NRMSE_i's over the patients. Similarly, we also define σ_{NEi} as the standard deviation of the normalized tracking errors $e^i(t) = (y_p^i(t) - y_m^i(t))/y_m^i(t)$ for patient i, and σ_{NE} as the average of σ_{NEi}'s over the patients.

Furthermore, to illustrate the percentage of PTT outliers which are outside clinically safe bounds, i.e., not in the interval $[y_m(t) - 10, y_m(t) + 10]$ during the transient and not in the interval $[60s, 80s]$ in steady-state, the Risk Percentage (RP) for patient i is defined as

$$\mathrm{RP}_i = \frac{N_i^{risk}}{T_i},$$

where N_i^{risk} is the number of time instants $t_i^1, \ldots, t_i^{T_i}$ at which the PTT value of patient i is outside the safe bounds. Then, RP is defined as the average of RP_i's over patients. We note that this metric is from a clinical perspective the most important in assessing the efficacy of our methods. Table I reports the performance of the MRC law for the patients in the test set.

TABLE I
PERFORMANCE OF THE MODEL REFERENCE CONTROL (TEST SET)

	value
RMSE	0.84
σ_E	0.82
NRMSE	1.20%
σ_{NE}	1.17%
RP	0%

In summary, in the case that model parameters are known, the MRC law tracks the reference signal quite well as demonstrated by the low RMSE and NRMSE. The RP value is zero, which completely assures clinical safety. The corresponding standard deviations for RMSE and NRMSE are small as well.

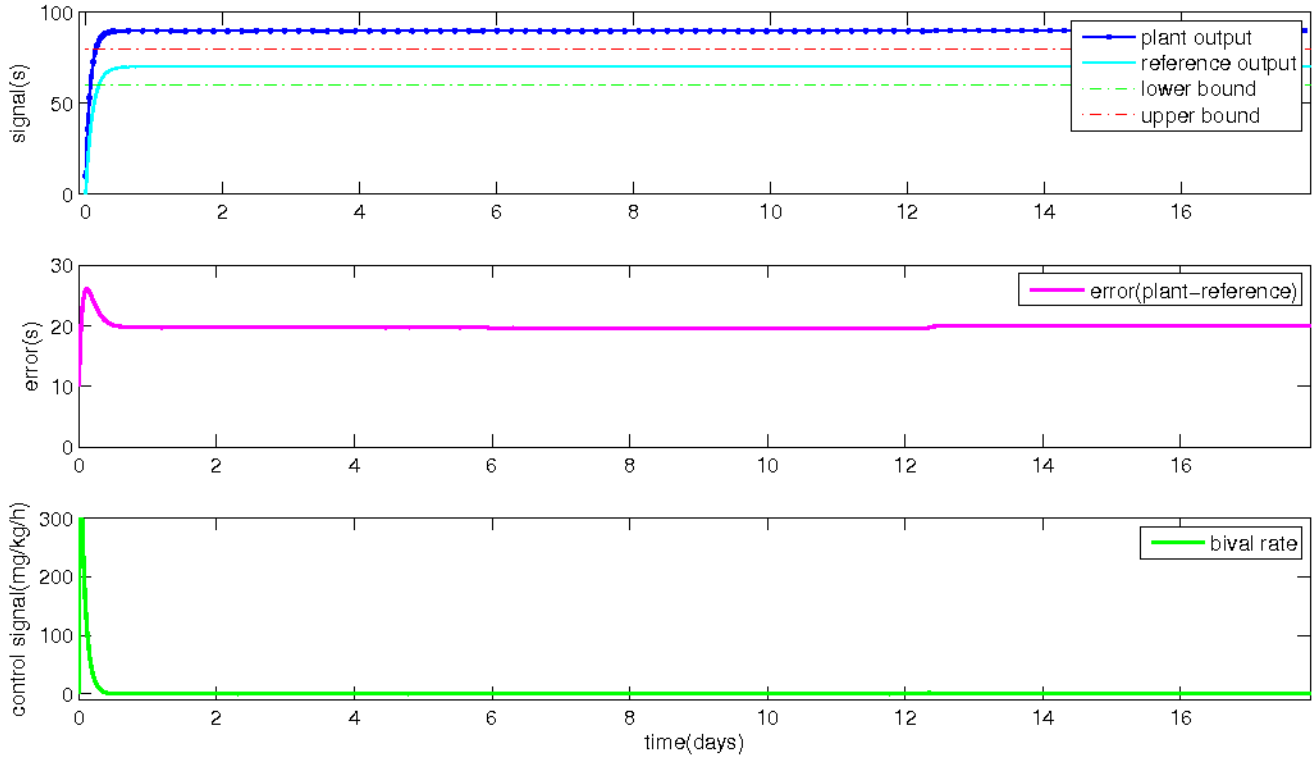

Fig. 5. The MRC law derived for one patient but applied to another patient.

B. Indirect Model Reference Adaptive Control (MRAC)

As we mentioned in the Introduction, there is significant patient variability in the response to bivalirudin. We have already established [1], that adapting model parameters to individual patients leads to improved performance. This suggests that the model structure is largely accurate but model parameters of an individual patient can deviate from population-wide parameter values.

TABLE II
PERFORMANCE OF THE INACCURATE MODEL REFERENCE CONTROL (TEST SET)

	value
RMSE	9.93
σ_E	3.98
NRMSE	14.18%
σ_{NE}	5.68%
RP	61.60%

To better assess the effect of this variability, we test the performance of the MRC law derived using parameter values of a specific patient when applied to another patient with different model parameters. Fig. 5 plots the MRC law performance for such a case. The top figure shows that there exists a large gap between the reference output signal and the system output signal. In addition, the system output is outside the safe range.

We also tested the MRC law derived using parameter values of a specific patient against all patients in the test set. Table II reports the results. We note that RMSE, NRMSE, and RP are substantially higher (and clinically unacceptable) than those in Table I. The difference of course is due to the fact the results of Table I are obtained when using the MRC law with the correct model parameters for each patient, whereas Table II results apply the MRC law with parameters of some patient to another patient. The small values of σ_E and σ_{NE} in Table II indicate that performance of the MRC law when used with the wrong parameters is consistently poor. This situation should obviously be avoided because overdosing or underdosing is very dangerous for the patients.

To address this important issue, we next develop a method that first estimates the individual model parameters, and then adopts the MRC law we introduced using a certainty equivalence principle [13]. Such a control scheme is called indirect *Model Reference Adaptive Control (MRAC)* law.

By adding and subtracting $-a_m y_p(t)$ to (4), we can obtain the *State-Space Parametric Model (SSPM)*:

$$\dot{y}_p(t) = -a_m y_p(t) + (a_m - \beta_3) y_p(t) + \beta_1 \beta_2 u(t) + \beta_3 d(t). \quad (9)$$

Based on (9), the series-parallel estimation model [14] is given by:

$$\dot{\widehat{y}}_p(t) = -a_m \widehat{y}_p(t) + (a_m - \widehat{\beta}_3(t)) y_p(t) + \widehat{\beta}_1(t)\widehat{\beta}_2(t) u(t) + \widehat{\beta}_3(t) d(t), \quad (10)$$

where $\widehat{y}_p(t)$ is an estimated value of $y_p(t)$, and $\widehat{\beta}_1(t)$, $\widehat{\beta}_2(t)$, $\widehat{\beta}_3(t)$ are estimates of the system parameters β_1, β_2, and β_3 at time t. Note that in (10), $y_p(t)$ is treated as an input available for measurement. By using the certainty equivalence principle

(cf. (8)), we take the control scheme structure to be:

$$u(t) = -k_1(t)y_p(t) + k_2(t)r(t) - k_3(t)d(t), \qquad (11)$$

where

$$k_1(t) = \frac{a_m - \widehat{\beta}_3(t)}{\widehat{\beta}_1(t)\widehat{\beta}_2(t)}, \quad k_2(t) = \frac{b_m}{\widehat{\beta}_1(t)\widehat{\beta}_2(t)},$$

$$k_3(t) = \frac{\widehat{\beta}_3(t)}{\widehat{\beta}_1(t)\widehat{\beta}_2(t)}.$$

In this problem, we will estimate the product of $\beta_1(t)$ and $\beta_2(t)$ instead of estimating them separately. The model estimation error is $e(t) = y_p(t) - \widehat{y}_p(t)$ which implies:

$$\begin{aligned}\dot{e}(t) =& \dot{y_p}(t) - \dot{\widehat{y}}_p(t)\\ =& -a_m e(t) + \tilde{\beta}_3(t)(y_p(t) - d(t)) - \tilde{\beta}_{12}(t)u(t), \end{aligned} \qquad (12)$$

where

$$\tilde{\beta}_3(t) = \widehat{\beta}_3(t) - \beta_3, \qquad \tilde{\beta}_{12}(t) = \widehat{\beta}_1(t)\widehat{\beta}_2(t) - \beta_1\beta_2. \quad (13)$$

We now choose a Lyapunov-like function

$$V(t) = \frac{1}{2}e(t)^2 + \frac{1}{2\gamma_1}\tilde{\beta}_3(t)^2 + \frac{1}{2\gamma_2}\tilde{\beta}_{12}(t)^2, \qquad (14)$$

which, with γ_1, $\gamma_2 > 0$, is non-negative for all t. By taking the derivative on both sides of (14) we obtain

$$\begin{aligned}\dot{V}(t) =& e(t)\dot{e}(t) + \frac{1}{\gamma_1}\tilde{\beta}_3(t)\dot{\tilde{\beta}}_3(t) + \frac{1}{\gamma_2}\tilde{\beta}_{12}(t)\dot{\tilde{\beta}}_{12}(t)\\ =& -a_m(e(t))^2 + \tilde{\beta}_3(t)\left[e(t)(y_p(t) - d(t)) + \frac{1}{\gamma_1}\dot{\tilde{\beta}}_3(t)\right]\\ &+ \tilde{\beta}_{12}(t)\left[\frac{1}{\gamma_2}\dot{\tilde{\beta}}_{12}(t) - e(t)u(t)\right]. \end{aligned} \qquad (15)$$

Then, choosing

$$\dot{\tilde{\beta}}_3(t) = -\gamma_1(y_p(t) - d(t))e(t) \text{ and } \dot{\tilde{\beta}}_{12}(t) = \gamma_2 e(t)u(t)$$

leads to $\dot{V}(t) = -a_m e(t)^2 \leq 0$. In addition, since $\beta_1\beta_2$ and β_3 are constants, (13) implies $\dot{\tilde{\beta}}_3(t) = \dot{\widehat{\beta}}_3(t)$ and $\dot{\tilde{\beta}}_{12}(t) = d(\widehat{\beta}_1(t)\widehat{\beta}_2(t))/dt$. It follows that we could estimate the model parameters by:

$$\begin{aligned}\widehat{\beta}_3(t + \Delta t) &= \widehat{\beta}_3(t) + \dot{\widehat{\beta}}_3(t)\Delta t,\\ \widehat{\beta}_{12}(t + \Delta t) &= \widehat{\beta}_{12}(t) + \tfrac{d(\widehat{\beta}_1(t)\widehat{\beta}_2(t))}{dt}\Delta t,\end{aligned} \qquad (16)$$

for small Δt. Then, we can adapt the controller coefficients recursively and control the system in real-time by using (cf. (11))

$$u^*(t) = -\frac{a_m - \widehat{\beta}_3(t)}{\widehat{\beta}_{12}(t)}y_p(t) + \frac{b_m}{\widehat{\beta}_{12}(t)}r(t) - \frac{\widehat{\beta}_3(t)}{\widehat{\beta}_{12}(t)}d(t). \quad (17)$$

Similarly, as we did earlier for the MRC law, we will use the control $\max\{0, u^*(t)\}$ to avoid negative values.

Theorem III.2 *Under the control law (17), the tracking error converges to* 0 *as* $t \to \infty$.

Proof: By choosing such control law, $\dot{V}(t) = -a_m e(t)^2 \leq 0$, $\forall t > t_0$. Since $V(t)$ is bounded from below and non-increasing, it converges to a constant. This implies that $-a_m \int_{t_0}^{\infty} e^2(t)dt = V(\infty) - V(t_0)$ is bounded, which in turn implies that $e(t) \to 0$ as $t \to \infty$ according to Barbalat's lemma [15]. It also follows that $\dot{\tilde{\beta}}_3(t)$, $\dot{\tilde{\beta}}_{12}(t) \to 0$ as $t \to \infty$. ■

One key flaw of the adaptive control law (17) is that the boundness of control signal $u(t)$ can not be established unless we show that $k_1(t)$, $k_2(t)$, $k_3(t)$ are all bounded. However, such a control law may generate estimates of $\beta_1\beta_2$ arbitrarily close or even equal to zero, which leads to the uncontrollability of the estimated model and unboundness of $u(t)$. To avoid this issue, we propose a modification to the control law (17). One method is to modify the adaptive law for $\widehat{\beta}_{12}(t)$ so that adaptation takes place in a subset of $\mathbb{R}$ which does not include the zero element. We need to use the a priori knowledge of $\beta_1 \geq \beta_1^{lb} > 0$ and $\beta_2 \geq \beta_2^{lb} > 0$ to do the projection:

$$\begin{aligned}\dot{\tilde{\beta}}_3(t) =& -\gamma_1(y_p(t) - d(t))e(t),\\ \dot{\tilde{\beta}}_{12}(t) =& \begin{cases}\gamma_2 e(t)u(t), & \text{if } |\tilde{\beta}_{12}(t)| > \beta_1^{lb}\beta_2^{lb},\\ & \text{or } |\tilde{\beta}_{12}(t)| = \beta_1^{lb}\beta_2^{lb}\\ & \text{and } e(t)u(t)\text{sgn}(\tilde{\beta}_{12}(t)) \geq 0,\\ 0, & \text{otherwise.}\end{cases}\end{aligned} \qquad (18)$$

After modifying the adaptive control law, the time derivative of the Lyapunov function becomes:

$$\dot{V}(t) = \begin{cases}-a_m(e(t))^2, & \text{if } |\tilde{\beta}_{12}(t)| > \beta_1^{lb}\beta_2^{lb},\\ & \text{or } |\tilde{\beta}_{12}(t)| = \beta_1^{lb}\beta_2^{lb}\\ & \text{and } e(t)u(t)\text{sgn}(\tilde{\beta}_{12}) \geq 0,\\ -a_m(e(t))^2 & \\ +\tilde{\beta}_{12}(t)e(t)u(t), & \text{if } |\tilde{\beta}_{12}(t)| = \beta_1^{lb}\beta_2^{lb}\\ & \text{and } e(t)u(t)\text{sgn}(\tilde{\beta}_{12}(t)) < 0.\end{cases}$$

Therefore, $\dot{V}(t) \leq -a_m e^2(t) \leq 0$, $\forall t \geq t_0$.

Using a similar argument as before, it can be shown that by using this modified parameter estimation law (18), the tracking error converges to zero driven by a bounded control signal. Additionally, we have shown (cf. Thm. III.1) that the reference output response is exponentially stable, and it follows that the system output can be driven to the stable state exponentially fast.

We next test the indirect MRAC law using the patient data. The parameter values of the reference model are the same as in Sec. III-A. We choose the population-wide parameter values $\beta_3^* = 7.9 \times 10^{-4}$, and $\beta_1^*\beta_2^* = 4.22$ as initial values of $\widehat{\beta}_3(t)$ and $\widehat{\beta}_{12}(t)$, respectively. The MRAC adapts based on these estimates in real-time. We also set $\gamma_1 = \gamma_2 = 5 \times 10^{-4}$. The trajectory of the system under the indirect MRAC is shown in Fig. 6.

Fig. 6 indicates that the system output quickly converges to the reference output and it remains within the desired range (top figure). The tracking error oscillates around zero (middle figure), but it is not as smooth as in Fig. 4. This is due to the fact that the indirect MRAC takes some time to estimate the system parameters first and then adapts the controller coefficients. Similarly, we can also obtain the bivalirudin infusion rate (bottom figure). Notice that although $d(t)$ changes

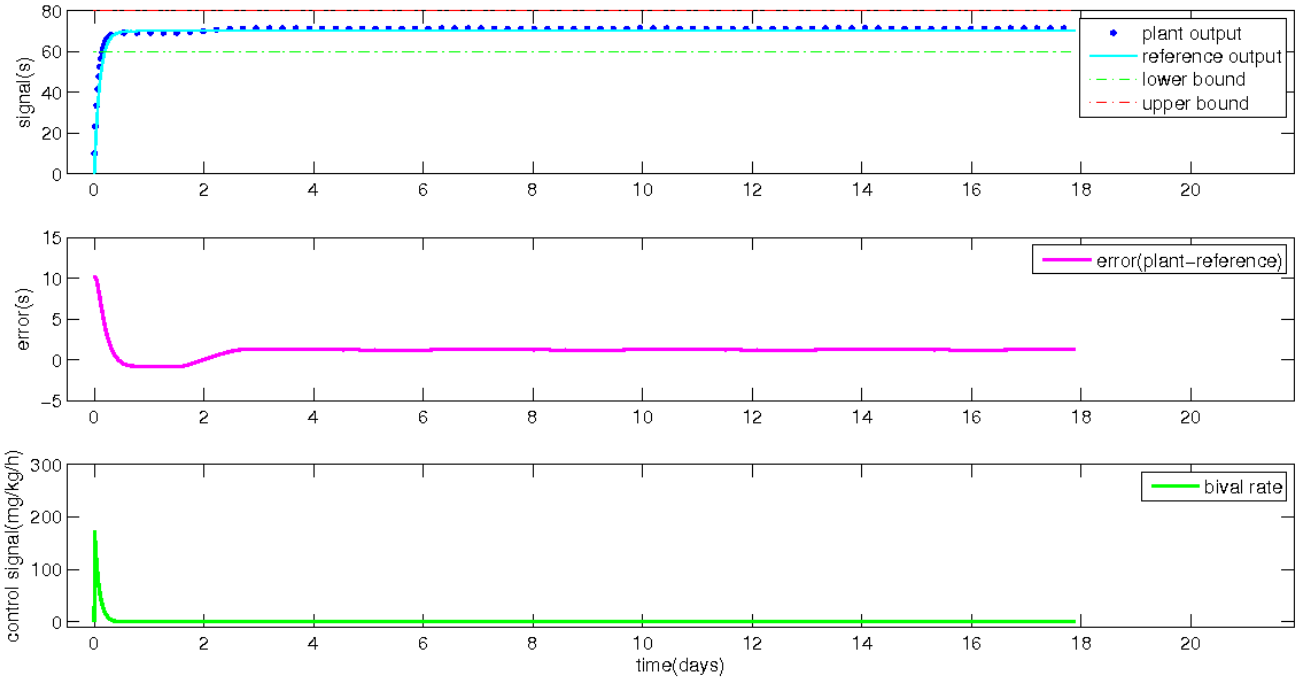

Fig. 6. The performance of the indirect MRAC law.

over time, the control signal can drive the system to track the reference output signal well. The performance of indirect MRAC for all patients in the test set is reported in Table III.

TABLE III
PERFORMANCE OF THE INDIRECT MODEL REFERENCE ADAPTIVE CONTROL (TEST SET)

	value
RMSE	5.52
σ_E	2.00
NRMSE	7.88%
σ_{NE}	2.86%
RP	2.30%

We note that in this case, the values of our three performance metrics are all higher than those in the Table I. This is again explained by the fact that adaptation of the indirect MRAC law is not very fast due to the parameter estimation step. Yet, RMSE, NRMSE and RP values are now significantly less than those in Table II and they could be considered acceptable in a clinical setting.

C. Direct Model Reference Adaptive Control MRAC

In this section, we focus on designing the direct MRAC without estimating the model parameters first. Because the individual model parameters are unknown, we can not apply the MRC law directly. Based on the structure of MRC law, we propose an adaptive control law with similar structure:

$$u(t) = -\widehat{k}_1(t)y_p(t) + \widehat{k}_2(t)r(t) - \widehat{k}_3(t)d(t),$$

where $\widehat{k}_1(t)$, $\widehat{k}_2(t)$, and $\widehat{k}_3(t)$ are the estimates of MRC controller coefficients k_1^*, k_2^*, and k_3^* at time t, respectively. We will devise a control law that estimates these coefficients directly.

Consider the error derivative:

$$\begin{aligned}\dot{e}(t) =& \dot{y}_p(t) - \dot{y}_m(t)\\ =& -a_m e(t) + \beta_1\beta_2[-\tilde{k}_1(t)y_p(t)\\ &+ \tilde{k}_2(t)r(t) - \tilde{k}_3(t)d(t)],\end{aligned}$$

where $\tilde{k}_i(t) = \widehat{k}_i(t) - k_i^*, i = 1, 2, 3$. It follows that $\dot{\tilde{k}}_i(t) = \dot{\widehat{k}}_i(t), i = 1, 2, 3$.

To design the controller, consider the Lyapunov-like function:

$$V(t) = \frac{e(t)^2}{2} + \beta_1\beta_2\left[\frac{\tilde{k}_1(t)^2}{2\gamma_1} + \frac{\tilde{k}_2(t)^2}{2\gamma_2} + \frac{\tilde{k}_3(t)^2}{2\gamma_3}\right].$$

By taking the derivative, we obtain:

$$\begin{aligned}&\dot{V}(t)\\ &= \dot{e}(t)e(t) + \beta_1\beta_2\left[\frac{\tilde{k}_1(t)\dot{\tilde{k}}_1(t)}{\gamma_1} + \frac{\tilde{k}_2(t)\dot{\tilde{k}}_2(t)}{\gamma_2} + \frac{\tilde{k}_3(t)\dot{\tilde{k}}_3(t)}{\gamma_3}\right]\\ &= -a_m e^2(t) + \beta_1\beta_2\left[\frac{\tilde{k}_1(t)}{\gamma_1}(\dot{\tilde{k}}_1(t) - e(t)\gamma_1 y_p(t))\right.\\ &\left. + \frac{\tilde{k}_2(t)}{\gamma_2}(\dot{\tilde{k}}_2(t) + e(t)\gamma_2 r(t)) + \frac{\tilde{k}_3(t)}{\gamma_3}(\dot{\tilde{k}}_3(t) - e(t)\gamma_3 d(t))\right],\end{aligned}$$

where we have the a priori knowledge that $\beta_1\beta_2 > 0$.

Choosing

$$\begin{aligned}\dot{\tilde{k}}_1(t) =& \gamma_1 e(t)y_p(t),\\ \dot{\tilde{k}}_2(t) =& -\gamma_2 e(t)r(t),\\ \dot{\tilde{k}}_3(t) =& \gamma_3 e(t)d(t),\end{aligned}$$

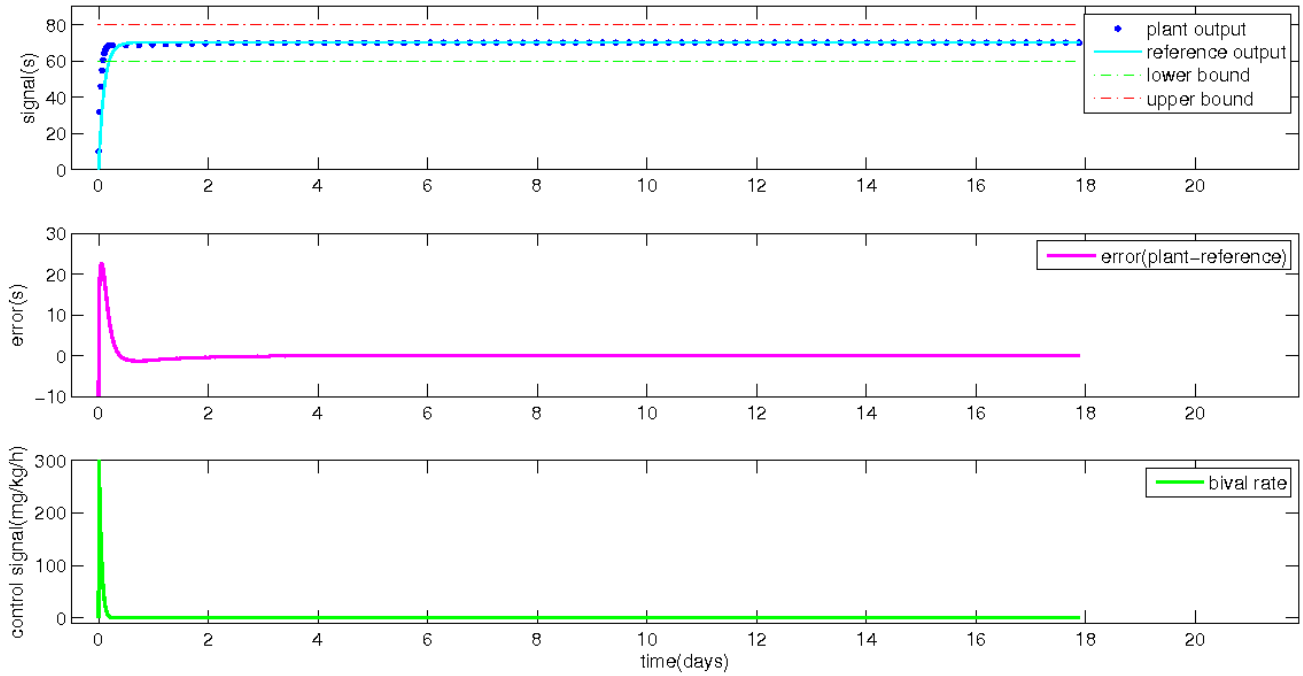

Fig. 7. The performance of direct MRAC law.

leads to $\dot{V}(t) = -a_m e(t)^2 \leq 0$. Furthermore, the controller coefficients can be adapted by

$$\widehat{k}_i(t + \Delta t) = \widehat{k}_i(t) + \dot{\widehat{k}}_i(t)\Delta t, \qquad i = 1, 2, 3,$$

and our direct MRAC controller becomes

$$u(t) = -\widehat{k}_1(t)y_p(t) + \widehat{k}_2(t)r(t) - \widehat{k}_3(t)d(t). \qquad (19)$$

As with the previous two controllers, we will use $\max\{0, u(t)\}$ to avoid negative controls.

We establish the following result; we omit the proof because it is similar to the proof of Theorem III.2.

Theorem III.3 *Under the control law (19), the tracking error converges to* 0 *as* $t \to \infty$.

We know that the reference model output is exponentially stable and the tracking error converges to zero as t increases, which establishes that the system output can be driven to track the reference output well. To avoid overdosing and underdosing risks that may occur in the time it takes the MRAC to converge to the appropriate controller parameters, we can use as initial estimates of these coefficients the MRC coefficients, namely $\widehat{k}_1(0) = 2.37$, $\widehat{k}_2(0) = 165.75$, and $\widehat{k}_3(0) = 1.87 \times 10^{-4}$, obtained from a system model parametrized with population-wide parameters.

We applied such a direct MRAC law to the same patient used for generating Fig. 6. The result is shown in Fig. 7 (using $\gamma_1 = \gamma_2 = \gamma_3 = 0.001$). We note that driven by the direct MRAC law, the system output quickly converges to the reference output. Although the system output oscillates around the reference signal, it remains within the desired range (top figure). The tracking error also converges to zero (middle figure). We also plot the bivalirudin infusion rate (bottom figure). Compared to the indirect MRAC, the direct MRAC has similar performance on controlling the PTT. However, the direct MRAC avoids parameter estimation and estimates controller parameters directly.

Table IV reports the overall performance of the direct MRAC for the patients in the test set. Compared to the results from the indirect MRAC, the direct MRAC achieves lower values for all performance metrics, i.e., RMSE, NRMSE, σ_E, σ_{NE} and RP. Notice the rather significant decrease of the RP value, which, as we argued, is clinically a top priority. This table validates the fact that the direct MRAC is a more efficient and safer control scheme than the indirect MRAC.

TABLE IV
PERFORMANCE OF THE DIRECT MODEL REFERENCE ADAPTIVE CONTROL (TEST SET)

	value
RMSE	0.80
σ_E	0.80
NRMSE	1.15%
σ_{NE}	1.14%
RP	0.09%

IV. CONCLUSIONS

Based on a specific dynamic system model of bivalirudin acting in cardiac surgical patients, we developed two methods for synthesizing a controller to regulate the bivalirudin infusion rate and induce a PTT within a desirable range. The first method assumes that the model parameters are available and develops a control law that tracks a physician specified reference output signal. Our second method considers patients

for which past clinical records are sparse and accurate model parameters are not readily available. It develops an indirect control scheme (indirect MRAC) that first estimates the model parameters and then adapts the corresponding controller based on these estimates. Alternatively, a direct control scheme (direct MRAC) that adapts the controller without estimating the model parameters first is also developed. Testing of these schemes against actual patient data from a hospital, shows that the direct MRAC is more efficient than the indirect version.

The methods we developed can be seen as key steps towards automation of dosage decisions in a hospital setting, which can help eliminate errors and neutralize the inexperience of residents who are currently responsible for these decisions.

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APPENDIX

The solution to Eq. (5) is

$$y_m(t) = \Phi(t, t_0) y_m(t_0) + \int_{t_0}^{t} \Phi(t, \tau) b_m r(\tau) d\tau,$$

where $\Phi(t, \tau) = e^{-a_m(t-\tau)}$ is the state transition function in this problem. Since $r(t) = C_r$, which is a constant, the solution to (5) can be written as

$$y_m(t; t_0, y_m(t_0)) = e^{-a_m(t-t_0)} \left(y_m(t_0) - \frac{b_m C_r}{a_m} \right) + \frac{b_m C_r}{a_m}. \quad (20)$$

Equation (20) indicates that $y_m(t; t_0, y_m(t_0)) \to \frac{b_m C_r}{a_m}$ which is a constant, as $t \to \infty$. In addition, using Definition 1, it can be easily verified that $y_{me} = \frac{b_m C_r}{a_m}$ is the equilibrium state of our reference system. Furthermore, $|y_m(t; t_0, y_m(t_0)) - y_{me}| = |e^{-a_m(t-t_0)}(y_m(t_0) - y_{me})| = |y_m(t_0) - y_{me}| e^{-a_m(t-t_0)}, \forall t \geq t_0$. Therefore, by Definition 2, it follows that the reference model equilibrium state y_{me} is exponentially stable.

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